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AFOEHL REPORT 90-030CA00156BPA

Sample Collection, Analysis, and Respirator Use With Isocyanate Paints

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February 1990

Final Report

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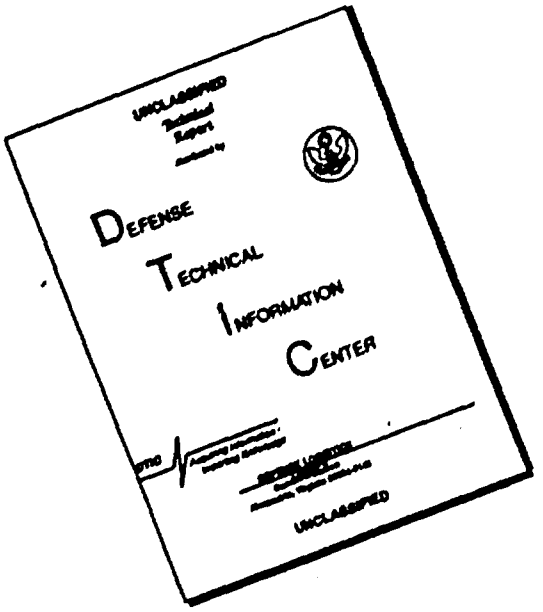

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UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS N/A
2a. SECURITY CLASSIFICATION AUTHORITY N/A	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release. Distribution is unlimiter.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE N/A	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) AFOEHL Report 90- 030CA00156BPA	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION AF Occupational and Environmental Health Laboratory 6b. OFFICE SYMBOL (If applicable) CA	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) Brooks AFB TX 78235-5501	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Same as 6a 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) Same as 6c	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO / PROJECT NO / TASK NO / WORK UNIT ACCESSION NO
11. TITLE (Include Security Classification) Sample Collection, Analysis, and Respirator Use with Isocyanate Paints (U)	
12. PERSONAL AUTHOR(S) Col Bruce J. Poitrast; Capt David Carpenter	
13a. TYPE OF REPORT Final 13b. TIME COVERED FROM ___ - ___ TO ___ - ___	14. DATE OF REPORT (Year, Month, Day) February 1990 15. PAGE COUNT 49
16. SUPPLEMENTARY NOTATION	

17. COSATI CODES		
FIELD	GROUP	SUB-GROUP

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
Foams, Spray Painting, Patrick AFB
Mists, Vapors, Isocyanates, Respirators, Test and Evaluation (TG)

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This report was written in response to questions from field operations which indicated problems with regard to the health effects and respiratory protection required for isocyanate paints. Personnel sample results were not in keeping with observed levels of exposure in spray operations. Not all isocyanate toxicity is the result of sensitization. Often, the acute irritative effects of isocyanates are confused with those caused by sensitization. Sensitization occurs in 10% of users in most reports. The outside figure is 20%. The isocyanate moiety is not the only sensitizer in isocyanate paints. The paints may also contain amines and phenol derivatives which can be potent sensitizers. Current sampling and analytical methods for isocyanate do not reflect the environment when spray guns are in use. The majority of the isocyanate is missed. As currently accomplished these do not account for the isocyanate in the aerosol. The use of air supplied respirators as the most effective protective measure is discussed.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Col Bruce J. Poitrast	22b. TELEPHONE (Include Area Code) (512) 536-2002/AV 240 22c. OFFICE SYMBOL AFOEHL/CA

DD Form 1473, JUN 86 *Previous editions are obsolete*

SECURITY CLASSIFICATION OF THIS PAGE

UNCLASSIFIED

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ACKNOWLEDGMENTS

The assistance of Major Edward Guida in writing this report is gratefully acknowledged.

Contents

I. INTRODUCTION

Purpose: This report is written to clarify the problems with current sampling and analytical techniques for isocyanates in spray painting operations.

Problem: The obvious disconnect between observable levels of paint aerosol and the levels of isocyanate detected in paint spray environments led to questions regarding the utility of analytical and sampling methods.

Scope: We will address the following issues: respirator choice, sensitization, analytical and sampling technics.

II. DISCUSSION

Much effort has gone into attempts to control isocyanate vapor by pre-polymerizing most of the monomer in the manufacturing process. Even though this is done, the resulting polymer is still an isocyanate and has isocyanate toxic and sensitizing potential. If brought in contact with the lung, both acute toxic and sensitizing reactions may occur. Since the aerosol contains both free and polymerized active isocyanates, it must be prevented from reaching the respiratory tract and skin. Adequate information exists to justify the belief that vapor, aerosols, and dust from the isocyanates can sensitize.(1,2,3,4,5) Longley (2) reports acute toxicity in twelve men 120 feet downwind from a spray operation with a methylene bisphenyl isocyanate (MDI) paint. They suffered the acute, irritative asthma which can be expected from contact with high levels of the isocyanates. Since The vapor pressure of MDI is quite low (5×10^{-6} torr) the cause of toxicity was most likely aerosol.(5) White (6) reports on upholstery workers in a car factory who suffered asthma attacks. They cut and sewed isocyanate foams. Isocyanate vapor concentration from personal samples was 0.003 PPM. Foam particulate may have been the problem. Patty's (4) notes that polyurethane foam particulate is capable of producing lung sensitivity in animals. To some degree this is may be related to amines in the reacted polymer rather than any remaining unreacted isocyanate, but that can't be all of the problem because a sensitivity does develop to the isocyanate moiety. This reaction is worth keeping in mind because there is an enamel paint on the market which is used by our maintenance people that contains isocyanate and comes in a spray can. They do not list isocyanate on the MSDS because they believe that no sensitivity can result because they place fully reacted polymer in the paint. This is not the case. All precautions that apply to other isocyanates apply to this one. Zenz (1) states that isocyanates may enter the respiratory tract as dusts and aerosols as well as vapor and cause sensitization. Some of the variability in exposure levels below which no sensitivity to isocyanate was found (from 0.003 to 0.07 PPM) may be accounted for by failure to include isocyanate aerosol and dust, in the measurement.(3,7,8,9,10,11,12) When the foregoing factors are considered and added to the problems with collection and analysis which are detailed below it becomes obvious that the professional judgment of the members of the occupational health team is the critical factor

in determining the level of protection required, not the number reflected in the sampling result.

The analytical method used by the Air Force and OSHA Method 42 are based on NIOSH Method 2535. NIOSH 2535 is based on OSHA/NIOSH method 5505. Let us first consider 5505 (see Appendix B). This is the impinger method. On page 1 of 5505 there is a block titled accuracy which contains the following, "The range of usefulness has not been studied. The bias has not been determined. The precision has not been evaluated." In a block labelled applicability on page 1, the statement would lead you to believe that this method is good for any form of isocyanate; however, on page 4, in a block labelled evaluation method, we find that the method was evaluated using monomeric toluene diisocyanate. Thus there is no data to justify its use except with monomers. Subsequent testing at NIOSH determined that the method did not accurately measure anything but monomer, and not that if it was inhibited. In belated recognition of this fact, NIOSH retracted the method in the September 1987 Applied Industrial Hygiene.(17) It is difficult to tell which of the many problems with this method is the major problem when you read the retraction. All other methods are departures from this troubled method. On page 1 of 5505 under the block, "other methods" it says that other methods are for monomeric species only. Particular reference is made to P&CAM 326. OSHA 42/NIOSH 2535 is a revision of P&CAM 326. Most paints today are prepolymerized and could not be measured with these monomeric methods, even if they worked properly. When we address the OSHA 42/NIOSH 2535 method, we find that, in addition to being designed for uninhibited monomers, the flow rate is too low, one liter per minute, to effectively pick up aerosol. The effective capture velocity is 1.55 cm/sec at that flow rate (See Appendix A). This will miss the majority of aerosol. It is noted on page 4 of 2535 that the samplers were poor collectors of aerosol. They start off by saying that the method collected 90% of the aerosol; however, the 90% that is collected is in the range of 0 - 2.8μ. Spray from air guns starts at about 10μ, so little of the spray will be collected. Aerosol is a source of sensitization. Humans can readily inhale particles up to 60μ. The particles need not reach the lung to cause sensitization. Anywhere on the respiratory tract epithelium is sufficient. From the foregoing it can be seen that use of this method in a spray paint environment misses the vast majority of the isocyanate.

As we neared publication, NIOSH released a new method, 5521, for isocyanates. This method will not characterize aerosol environments either as the flow rate remains too low, one liter per minute. In the applicability statement of the method, it is noted that the method is qualitative only for polyisocyanates since it measures them low. This method adds nothing significant to the analytical armamentarium. A copy of the method has been added to Appendix B.

The methods were designed for use with uninhibited isocyanates. The days of uninhibited isocyanate paints ended in 1976. On page 11 of OSHA 42 under interferences, in 3.6.2 we find that amines, alcohols, phenols, carboxylic acids and anhydrides are interferences. Some of these are readily found in paint shops. Worse, some of them are actually in the modern paints. Because they interfere with isocyanate polymerization, they are used as inhibitors. Specifically amines, alcohols and phenols, among other chemicals, are used to

mask the isocyanate to prevent the polymerization reaction until a more active chemical knocks it off. This means they won't react in the test, as the inhibitor is more tightly bound to isocyanate than the test reagent. There is currently no method which will measure inhibited isocyanate. Unfortunately, the isocyanate will still cause sensitization. The inhibitors themselves are often toxic. They do not need to be listed on the paint labels because they have not been demonstrated to be toxic as used in the paint. Amines, phenols, and anhydrides are sensitizers.

To summarize, the test methods for isocyanate are designed for use with monomeric, uninhibited isocyanate in the vapor form. We almost never encounter uninhibited, monomeric isocyanate any more. Most of our paints today are blends of several types of prepolymerized isocyanates with both promoters and inhibitors. In today's paint even the monomer may be inhibited. As a result of the foregoing, our analytical methods are completely unable to characterize a spray paint environment. Only the professional judgement of the industrial hygienist has any value in this arena right now. The test results give a false sense of security, since they grossly underestimate the environment.

Other methods for measuring have been suggested in the AFOEHL Newsletter. The use of the percentage of isocyanate in the solid portion of the paint times the amount of aerosol measured as a nuisance dust is one suggested method. Another option is to sample for pigment. You will need the MSDS or some other source containing the following information for the paint in use: concentration of the pigment, isocyanate monomer and total isocyanate including biuret if any. Air sample for the pigment, mark the sample "pigment for isocyanate" and submit to AFOEHL/SA as usual. Based on the reported pigment concentration, the monomer and the total isocyanate concentration can be calculated by multiplying the pigment concentration by the isocyanate/ pigment ratio to determine the total isocyanates. The monomer can then be calculated by using the monomer percentage of the total isocyanates. Proper respiratory protection can be determined by making some conservative assumptions, and giving proper consideration to the circumstances and the calculations which follow. No air purifying respirator has been approved for use with isocyanates. This is because the odor threshold for isocyanates is 20 times the STEL and 80 times the TLV. Therefore no warning property exists which would indicate respirator failure. It is well known that charcoal canisters do not filter aerosol efficiently. As much as 50% of the chemicals present in the aerosol may easily pass directly through the filter. This necessitates the use of particulate pre-filters. It should also be noted that the presence of humidity may alter the efficiency of a filter. The useful lifetime of charcoal is reduced 50% by 30% relative humidity (RH) at room temperature. It is further reduced 50% by 70% RH at room temperature. Now, continuing our calculations, assume the monomer will completely volatilize while the polymer remains in the aerosol state. If the monomer calculates to greater than 0.005 mg/m^3, then airline respirators will be required. If not, then fullface, negative pressure, organic vapor cartridges with pre-filter can be used. Protection for the skin of the face is necessary because isocyanates are skin sensitizers and is better accomplished with the fullface respirator than it is with goggles. Since the isocyanates are skin sensitizers as well as lung sensitizers, protection must be afforded for the skin. This is

especially true since lung disease has been shown to develop as the result of skin exposure. Lung exposure can produce dermal sensitivity as well. Only a full face respirator or hood can protect the skin of the upper face from exposure.

Again, in summary, if air purifying respirators are to be used, then their use should be restricted to a minimum, and only fullface respirators with charcoal canisters and high efficiency pre-filters should be used. In an ongoing spray environment, only supplied air should be used. Short duration of operation should not be used as a reason to minimize protection. There is evidence that excursions of isocyanate may be more meaningful than averages in creating disease.(3,14) Hyperactive small airways disease has been documented in workers wearing organic vapor respirators exposed to the very low isocyanate levels of 0.002 PPM to 0.005 PPM. Some of these workers did not demonstrate subjective symptoms and so were unaware of their disease.(9,10) Commonly used text books of occupational health (1,13) state repeatedly that even where isocyanate vapor levels may not be a problem, if isocyanate is used in a spray operation, a serious hazard exists.

If there is concern that in spite of your best efforts a problem remains, then pulmonary function tests pre- and post-work may prove useful. A significant decrease in the FEF 25-75 between pre- and post-work tests, even in an asymptomatic individual, is cause to believe that sensitization has occurred. Immediate removal from work with isocyanates and referral for pulmonary workup is warranted.

III. CONCLUSIONS

The most certain respiratory protection for isocyanate paints is a supplied air respirator worn at any time an operation is in progress, regardless of application duration.

Unprotected individuals should be removed from any possibility of contact with overspray from spray operations. If spraying is done in an open area such as a hangar, it is not possible to adequately protect others in the hangar short of removing them or putting them in respirators.

Be extremely careful of downwind workers when spraying. Recorded episodes of severe, acute toxicity have occurred over 120 feet downwind.

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APPENDIX A

FLOW RATES NECESSARY FOR PARTICLE CAPTURE

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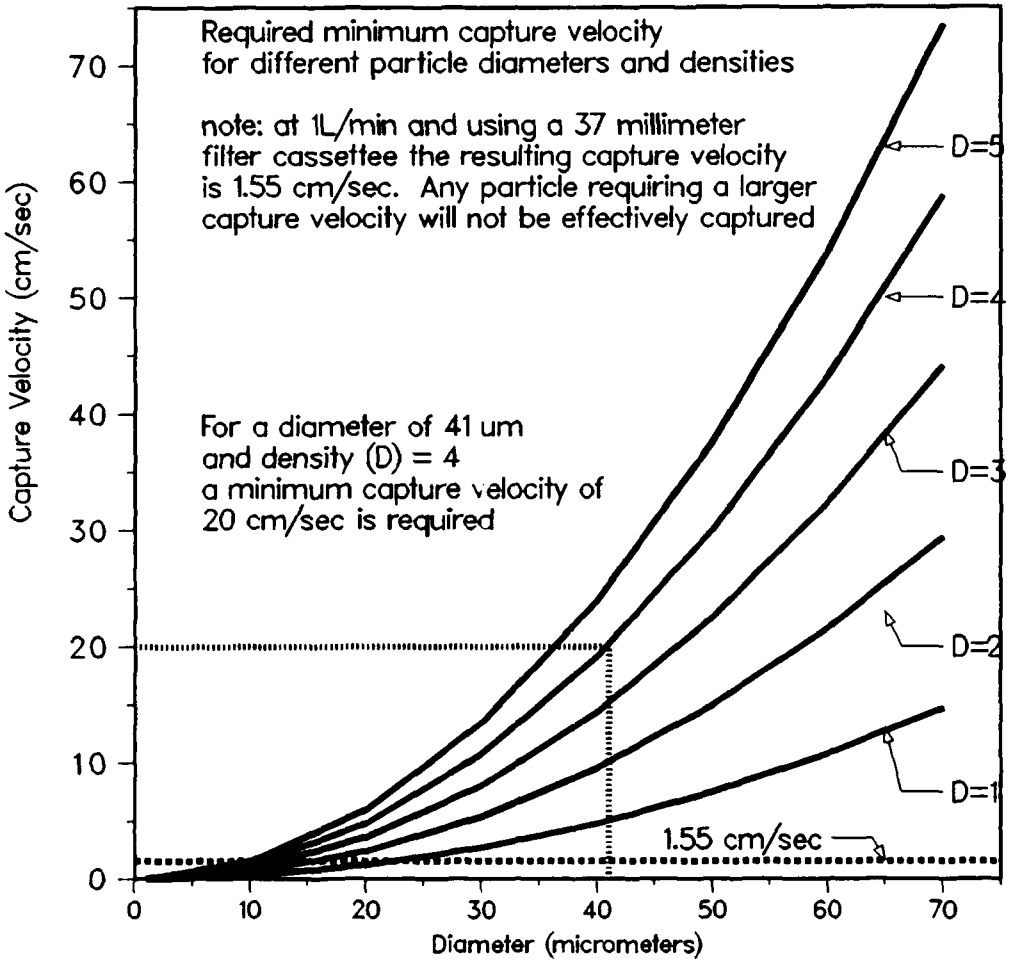
Required minimum capture velocity
for different particle diameters and densities
note: at 1L/min and using a 37 millimeter
filter cassettee the resulting capture velocity
is 1.55 cm/sec. Any particle requiring a larger
capture velocity will not be effectively captured
For a diameter of 41 um
and density (D) = 4
a minimum capture velocity of
20 cm/sec is required
D=5
D=4
D=3
D=2
D=1
1.55 cm/sec
Capture Velocity (cm/sec)
Diameter (micrometers)
0
10
20
30
40
50
60
70

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APPENDIX B

SAMPLING AND ANALYTICAL METHODS

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FORMULA: RNCO

ISOCYANATE GROUP

METHOD: 5505
ISSUED: 2/15/84

M.W.: varies

OSHA: C 20 ppb (MDI and TDI)
NIOSH: 5 ppb/10 hr; 20 ppb/10 min (diisocyanates) [1]
ACGIH: C 20 ppb (MDI); 5 ppm (TDI)

PROPERTIES: depend on R- to which isocyanate group is attached; R- may be aromatic, aliphatic, monomeric or polymeric

SYNONYMS: various [1], including 4,4'-methylenediphenyl isocyanate (MDI; CAS #101-68-8); 2,4-toluene diisocyanate (TDI; CAS #584-84-9).

SAMPLING

SAMPLER: IMPINGER
(solution of 1-(2-methoxyphenyl)-piperazine in toluene)

FLOW RATE: 1 L/min

VOL-MIN: 350 L
-MAX: 600 L

SHIPMENT: in vials; flammable liquid

SAMPLE STABILITY: $\geq$ 2 weeks

BLANKS: 2 to 10 field blanks per set + 1 initial reagent blank

ACCURACY

RANGE STUDIED: not studied

BIAS: not determined

OVERALL PRECISION (s_r): not evaluated

MEASUREMENT

!TECHNIQUE: HPLC, UV DETECTION
!
!ANALYTE: 1-(2-methoxyphenyl)piperazine
!
!PREPARATION: acetylate analyte; evaporate toluene; dissolve residue in methanol
!
!INJECTION VOLUME: 10 µL
!
!MOBILE PHASE: 50/50 acetonitrile/0.015 M sodium acetate; pH 6; 1.5 mL/min
!
!COLUMN: octylsilylated silica (C_8), 10-µm particle size, 25 cm x 4.2 mm
!
!DETECTOR WAVELENGTH: 254 nm
!
!CALIBRATION: solutions of 1-(2-methoxyphenyl)-piperazine in methanol
!
!RANGE: 0.24 to 3.5 µmol NCO group per sample
!
!ESTIMATED LOD: 0.2 µmol NCO group per sample
!
!PRECISION (s_r): 0.048 [2]

APPLICABILITY: This method is used to determine the total concentration of the isocyanate group, regardless of the molecule to which the isocyanate group is attached. Monomeric isocyanates can be individually determined with this sampling reagent [3]. Concentrations of ureas from monomeric isocyanates and 1-(2-methoxyphenyl)piperazine can be determined simultaneously. NIOSH has used this method to sample for isocyanate groups and monomeric 2,4-toluene diisocyanate in a urethane foam manufacturing plant.

INTERFERENCES: Phosgene, acid halides and possibly some esters will react with 1-(2-methoxyphenyl)piperazine, consume reagent, and cause a positive bias.

OTHER METHODS: P&CAM 141, 142, 326, and 347 [4,5,6] are for monomeric species only and which are subject to amine interference or use an unstable derivatizing agent. Recent reviews have been published [7,8].

REAGENTS:

1. Sampling medium:* 1-(2-methoxyphenyl)piperazine in toluene (see APPENDIX).
   NOTE: Reserve 10 mL of this solution for analysis (step 15).
2. Acetic anhydride.
3. Methanol.*
4. Acetonitrile.
5. Deionized water.
6. Pentane.
7. Sodium acetate, anhydrous.
8. Acetic acid, glacial.
9. Nitrogen.
10. Toluene.*
11. Calibration stock stolution, 1 µg/µL. Dissolve 1-(2-methoxyphenyl)piperazine in methanol.
12. Mobile phase. Dissolve 1.2 g sodium acetate in 1 L deionized water. Add 1 L acetonitrile. Add glacial acetic acid as needed to bring the pH to 6.0.

*See Special Precautions.

EQUIPMENT:

1. Sampler: midget impinger, 25-mL.
2. Personal sampling pump, 1 L/min, with flexible connecting tubing.
3. Glass-marking pen.
4. Liquid chromatograph with a UV detector, recorder, integrator and column (page 5505-1).
5. Ultrasonic waterbath.
6. Vials, 20-mL glass, with polypropylene-lined screw caps.
7. Vials, 4-mL glass, with screw caps.
8. Pasteur pipets, 7-cm glass, disposable.
9. Volumetric flasks, 10-mL.
10. Syringes, sizes appropriate for preparing standard solutions.
11. Pipets, 2- and 15-mL glass, delivery, with pipet bulb.
12. Hotplate.
13. Beakers, 250-mL.
14. Evaporator, Mini-Vap, 6 port, or equivalent.
15. Flask, filtration, 500-mL.
16. Funnel, Buchner, fritted glass, medium porosity, 100-mL.
17. Vacuum pump.
18. Flask, 50-mL, round bottom.
19. T-adapter, with stopcock.
20. pH meter.

SPECIAL PRECAUTIONS: Sample and standard preparation should be done in hood to avoid exposure to toluene and methanol vapors.

SAMPLING:

1. Calibrate each personal sampling pump with a representative sampler in line.
2. Transfer 15.0 mL sampling medium to an impinger. Mark the solution level on the impinger with a glass-marking pen.
3. Connect the assembled impinger to a sampling pump. If it is necessary to add solvent during sampling for proper impinger operation, add only toluene. Do not add more sampling medium.
   NOTE: If an area sample is being taken, the impinger may be packed in ice during sampling to retard toluene losses.
4. Sample 350 to 600 L of air at a sampling rate of 1 L/min.
5. Bring sample solution level back to the pre-sampling mark (15.0 mL) by adding toluene.
6. Transfer the sample solution to a 20-mL vial for shipment. Do not rinse the impinger.

SAMPLE PREPARATION:

7. Transfer a 2-mL aliquot to a 4-mL vial for evaporating.
8. Add 10 µL acetic anhydride to acetylate the 1-(2-methoxyphenyl)piperazine.
9. Evaporate toluene from sample under a stream of nitrogen while warming the sample on a 40 to 50 °C hotplate.

10. Add 200 µL methanol after sample has reached complete dryness.
11. Agitate sample in an ultrasonic bath for 15 min to dissolve residue.

CALIBRATION AND QUALITY CONTROL:

12. Prepare working standards (25 to 450 µg/mL) by adding appropriate aliquots of calibration stock solution to 2 to 3 mL methanol in a 10-mL volumetric flask. Add 10 µL acetic anhydride. Mix and dilute to the mark with methanol.
13. Analyze working standards together with samples and blanks (steps 16 through 18). Prepare a calibration graph of area vs. amount (µg) of 1-(2-methoxyphenyl)piperazine per 15 mL original solution.
    NOTE: The amount present in an original 15-mL sample is 1.5 times the concentration of the analyzed solution: (0.2 mL/aliquot) • (7.5 aliquots/sample).
14. Prepare control samples by adding a known amount of a monomeric isocyanate to 15.0 mL sampling medium and performing steps 7-11 and 16-19.
15. Analyze three 2-mL aliquots of the sampling medium from the same batch used for sampling (Reagent 1.).
    NOTE: These are not the same as field blanks.

MEASUREMENT:

16. Set up the HPLC system according to manufacturer's recommendations and to the conditions given on page 5505-1.
17. Inject a 10-µL concentrated sample aliquot.
18. Measure peak area.

CALCULATIONS:

19. Read amount, M_S (µg), of 1-(2-methoxyphenyl)piperazine per 15 mL sample from calibration graph for each sample.
20. Calculate the initial amount of reagent, µg, present before sampling, M_I, by averaging the amount determined for the three samples prepared from sampling medium not taken into the field (step 15).
21. Calculate the concentration of isocyanate groups, C (µmol/m³), in the air volume sampled, V (L):

$$C = \frac{(M_I - M_S) \cdot 10^3}{(192.26) \cdot (V)}, \ \mu mol/m^3.$$

where 192.26 is the molecular weight of 1-(2-methoxyphenol)piperazine.

EVALUATION OF METHOD:

Lab-tested with 2,4-toluene diisocyanate spiked samplers with independent quantitation of isocyanate groups from measurement of isocyanate urea [2]. The average recovery for the sample preparation procedure of 1-(2-methoxyphenyl)piperazine, as the acetyl derivative, was determined to be 96% over a range of 8.2 to 813 µg per 15-mL sample. Toluene solutions of 1-(2-methyoxyphenyl)piperazine (15.7 µg per 15-mL sample) were stored at room temperature for two weeks with no loss of 1-(2-methoxyphenyl)piperazine. Precision was determined from the analysis of 21 samples which were prepared by adding known quantities of monomeric 2,4-toluene diisocyanate (0.24 to 3.2 µmole) to 1-(2-methoxyphenyl)piperazine in toluene (43 µg/mL).

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APPENDIX:

PURIFICATION OF 1-(2-METHOXYPHENYL)PIPERAZINE AND PREPARATION OF SAMPLING MEDIUM:
Place 25 g 1-(2-methoxyphenyl)piperazine (yellowish white solid) in a 250-mL beaker. Add approximately 125 mL pentane. Bring to a boil on a hotplate and allow to boil until all but a small amount of yellow oil is in solution. The 1-(2-methoyphenyl)piperazine will melt as it is warmed in the pentane. Decant the solution into a clean beaker, cover with a watchglass and then cool in the freezer for 2 to 3 hrs. White fluffy crystals will form. Filter with a Buchner funnel. Transfer the crystals to a 50-mL round bottom flask and dry briefly under vacuum to remove final traces of pentane. Store the hygroscopic crystals in an air-tight container in a refrigerator. The melting range of the crystals is 26-29 °C.

Prepare the sampling medium using the purified 1-(2-methoxyphenyl)piperazine. Dissolve this reagent in toluene at a concentration of 43 µg/mL.

METHOD WRITTEN BY: Martha Seymour and A. W. Teass, Ph.D., NIOSH/DPSE.

FORMULA:  ; $C_9H_6N_2O_2$

TOLUENE-2,4-DIISOCYANATE

NIOSH METHOD: 2535

M.W.: 174.16

ISSUED: 8/15/87

OSHA: 0.02 ppm (ceiling)
NIOSH: 35 µg/m³/10 hrs; 140 µg/m³/10 min
ACGIH: TWA 0.005 ppm; STEL 0.02 ppm
(1 ppm = 7.12 mg/m³ @ NTP)

PROPERTIES: liquid; MP 19.5-21.5 °C; BP 251 °C; density 1.2244 g/mL @ 20 °C; VP ca. 1.3 Pa (0.01 mm Hg ; 0.96 mg/m³) @ 20 °C

SYNONYMS: 2,4-TDI; 2,4-bis(carbonylamino)toluene; CAS #584-84-9.

SAMPLING

SAMPLER: TUBE WITH REAGENT-COATED GLASS WOOL (N-[(4-nitrophenyl)methyl]-propylamine on glass wool)

FLOW RATE: 0.2 to 1 L/min

VOL-MIN: 2 L @ 0.14 mg/m³
-MAX: 170 L

SHIPMENT: protect from light

SAMPLE STABILITY: at least 14 days @ 25 °C [1]

STABILITY OF REAGENT ON GLASS WOOL:
≤ 7 days @ 25 °C; ≥ 4 weeks @ -21 °C

FIELD BLANKS: 10% of samples

ACCURACY

RANGE STUDIED: 0.039 to 0.53 mg/m³[1] (67-L samples)

BIAS: none found [1]

OVERALL PRECISION (s_r): 0.033 [1]

MEASUREMENT

TECHNIQUE: HPLC, UV DETECTION

ANALYTE: 3,3'-bis[(4-nitrophenyl)methyl]-3,3'-dipropyl-1,1'-(4-methyl-1,3-phenylene) diurea (2,4-TDIU)

RECOVERY: 2 mL CH_3OH; ultrasonic bath, 3 min

INJECTION VOLUME: 50 µL

MOBILE PHASE: 55:45 (v/v) CH_3CN:H_2O with 0.08% Et_3N and 0.16% H_3PO_4; 1.0 mL/min

DETECTOR: UV @ 254 nm

COLUMN: 25 cm x 4.6 mm; octadecylsilylated silica, 5-µm particle size

CALIBRATION: standard solutions of 2,4-TDIU in CH_3OH

RANGE: 0.3 to 25 µg 2,4-TDI per sample

ESTIMATED LOD: 0.1 µg 2,4-TDI per sample

PRECISION (s_r): 0.067 [1]

APPLICABILITY: The working range is 0.004 to 0.35 ppm (0.03 to 2.5 mg/m³) for a 10-L air sample. This method is applicable to isocyanate vapors (2,4-TDI vapor, 2,6-TDI vapor, and hexamethylene diisocyanate (HDI) vapor) [2,3], but not aerosols because of inefficient collection of aerosols and incomplete reaction of aerosol isocyanates with reagent.

INTERFERENCES: The reagent is slightly unstable in the dark at 25 °C. Tailing during HPLC, a result of reagent deterioration, may raise detection limits .

OTHER METHODS: This revises P&CAM 326 [4]. Sangö used similar HPLC conditions [5]. Melcher reviewed methods for isocyanates [6].

REAGENTS:

1. 2,4-TDI* (see APPENDIX B)
2. N-[(4-nitrophenyl)methyl]-propylamine hydrochloride
3. 2,4-TDIU (see APPENDIX B)
4. Methanol, chromatographic quality.
5. Calibration stock solution, 10 mg/mL. Dissolve 50 mg 2,4-TDIU in methanol to make 5 mL solution.
6. Water, distilled.
7. NaOH, 1 M.
8. Toluene, reagent grade.
9. Dichloromethane, reagent grade.
10. Hexane, reagent grade.*
11. Nitrogen, purified, compressed.
12. Mobile phase. Mix 0.8 mL triethylamine and 1.6 mL H_3PO_4 with 1 L 55:45 CH_3CN:H_2O (v/v).*
13. Dibutylamine, 99% pure.
14. Tetrahydrofuran, reagent grade.*
15. Bromocresol purple indicator solution.
16. HCl, 0.05 M, standardized.
17. 2,4-TDI stock solution, 100 mg/mL. Dissolve 500 mg 2,4-TDI in dichloromethane to make 5 mL solution.

*See SPECIAL PRECAUTIONS.

EQUIPMENT:

1. Sampler: glass tube, 8 cm x 6 mm ID, containing two sections of reagent-coated glass wool (see APPENDIX C); front section, 7 mm long; back section, 5 mm long. Reagent-coated glass wool is compressed tightly. Seal ends of sampler with plastic caps. Wrap middle section of sampler with black tape. Protect sampler from light. Sampler may be stored at -21 °C in the dark for at least four weeks. Limit period of storage of sampler at 25 °C in the dark to seven days.
2. Separatory funnels, 125-mL.
3. Beakers, 50- and 125-mL.
4. Aluminum foil.
5. Glass wool, silanized.
6. Glass rod, 15 cm x 4 mm.
7. Tweezers.
8. Glass tube with right-angle bend, 4.5 cm x 6 mm ID, wrapped with black tape.
9. Rubber tubing, opaque, 15 cm x ca. 8 mm ID.
10. Personal sampling pump, 0.2 to 1 L/min, with flexible connecting tubing.
11. High pressure liquid chromatograph, 254-nm UV detector, integrator, and column (page 2535-1).
12. Vials, glass, 2-mL, cap lined with PTFE.
13. Pipets, 2-, 15-, and 25-mL.
14. Ultrasonic bath.
15. Syringes, 100-µL, readable to 1 µL.
16. Syringes, 10-µL, readable to 0.1 µL.
17. Volumetric flasks, 5-mL.
18. Buret, 50-mL.
19. U-tube, glass, 25 cm x 15 mm ID, glass stopcocks.
20. Sorbent tube, glass, 7 cm x 6 mm, coconut shell charcoal, ca. 150 mg.

SPECIAL PRECAUTIONS: 2,4-TDI can irritate the eyes and skin, and can cause bronchial asthma and allergic eczema. Flash points of hexane, tetrahydrofuran and triethylamine are -26 °C, -17 °C, and -6 °C, respectively.

SAMPLING:

1. Calibrate each personal sampling pump with a representative sampler in line.
2. Remove plastic caps from sampler. Attach one end of glass tube with right-angle bend directly to inlet of sampler with short piece of opaque rubber tubing.
3. Sample 2 to 170 L of air at 0.2 to 1 L/min. Seal ends of sampler with plastic caps.

SAMPLE PREPARATION:

4. Transfer front and back sections of reagent-coated glass wool to separate vials. Add 2 mL methanol. Seal vials.
5. Place vials into ultrasonic bath for 3 min.

CALIBRATION AND QUALITY CONTROL:

6. Calibrate daily with at least five working standards over the range 0.3 to 80 µg 2,4-TDIU per sample (equivalent to 0.1 to 25 µg 2,4-TDI per sample).
   a. Prepare a series of standard solutions of 2,4-TDIU in methanol over the range of 0.15 to 40 µg/mL.
   b. Analyze together with samples and blanks (steps 8 and 9).
   c. Prepare calibration graph (peak area vs. µg 2,4-TDIU).
7. Determine recoveries from samplers in the range 0.3 to 25 µg 2,4-TDI per sample. Prepare three samples at each of three levels plus three media blanks.
   NOTE: Recoveries should be quantitative. If recoveries are not quantitative, attempt to determine the reason for error.
   a. Prepare a series of standard solutions of 2,4-TDI in dichloromethane in the range 0.06 to 5 mg/mL.
   b. Connect a U-tube to the inlet of a sampler with a short piece of tubing.
   NOTE: The length of tubing should be minimal to prevent losses of TDI by adsorption or reaction on the inside wall of the tubing.
   c. Connect charcoal sorbent tube to inlet of U-tube (charcoal can adsorb contaminants of air which would react with 2,4-TDI).
   d. Draw ambient air through the charcoal tube, U-tube, and sampler with a sampling pump at 1 L/min.
   e. Place 5 µL of a standard solution of 2,4-TDI into the U-tube.
   f. Allow operation of the pump to continue for 20 min.
   g. Analyze the sampler for 2,4-TDIU (steps 6 and 7 and 10 through 12).

MEASUREMENT:

8. Establish chromatographic conditions indicated on page 2535-1.
9. Inject sample aliquot manually or with autosampler. Measure peak area.

CALCULATIONS:

10. Determine the mass (µg) of 2,4-TDIU found on the sample front (W_f) and back (W_b) sections and in the average media blank front (B_f) and back (B_b) sections.
    NOTE: If $W_b > W_f/10$, report breakthrough and possible sample loss.
11. Calculate concentration, C, of 2,4-TDI in the air volume sampled, V (L):

$$C = \frac{0.310\ (W_f + W_b - B_f - B_b)}{V}\ mg/m^3,$$

where 0.310 = M.W. of 2,4-TDI/M.W. of 2,4-TDIU.

EVALUATION OF METHOD:

A variation of this method which involved normal-phase HPLC (Method P&CAM 326) was tested with fortified samplers and atmospheres generated with a diffusion cell [1,4]. Average recoveries of 2,4-TDIU from front sections of reagent-coated glass wool were 0.97 to 0.99 after applications of 1.0-, 2.1-, 9.9-, and 20.0-µg quantities of 2,4-TDI from a U-tube; s_r was 0.067 (21 samples, pooled). s_r was 0.033 (29 samples, pooled) for 67-L samples at 0.039 to 0.53 mg/m³. The independent method used for evaluation was that of Meddle and Wood [7]. Average concentrations ranged from 0.054 to 0.46 mg/m³ by the independent method [1]. Conclusive evidence for bias in the reagent-coated glass wool method was not found. Breakthrough volume was 71 L (0.53 mg/m³, 1 L/min); breakthrough volume was 279 L (0.14 mg/m³, 1 L/min). 2,4-TDIU was stable on coated glass wool at room temperature in the dark for 14 days. The reagent, N-[(4-nitrophenyl)methyl]propylamine, is unstable [1].

Evaluation of samplers with 2,4-TDI aerosols was not performed. However, samplers were inefficient collectors when aerosol particles were present in an atmosphere of 4,4'-methylenediphenylisocyanate (MDI). The collection efficiency of each sampler for MDI was about 90% (flow rate, 1 L/min; total concentration of MDI in vapor and aerosol forms, about 0.52 mg/m^3; mass median diameter of MDI particles, about 0.6 µm; geometric standard deviation, about 2.2) [1].

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METHOD REVISED BY: Samuel P. Tucker, Ph.D., NIOSH/DPSE.

APPENDIX A: Determination of Purity of 2,4-TDI

Dissolve 480 µL (365 mg, 0.00282 mole) dibutylamine in 10 mL tetrahydrofuran. Add 100 µL (122 mg, 0.000701 mole) 2,4-TDI. Stir the mixture and allow to stand 6 min. Add a few drops of bromocresol purple indicator solution. Prepare two additional samples in this manner. Titrate excess dibutylamine with 0.05 M HCl. Calculate percent purity, P, of 2,4-TDI for each sample:

$$P = \frac{(B - V \cdot M)}{2W} \cdot 100.$$

where: B = Molar quantity of dibutylamine before reaction (0.00282)
V = Volume of 0.05 M HCl (L)
M = Concentration of HCl (0.05M)
2 = Number of moles of dibutylamine required to react with 1 mole of 2,4-TDI
W = Molar quantity of 2,4-TDI added to tetrahydrofuran solution (0.000701)

APPENDIX B: Preparation of 2,4-TDIU [8]

Dissolve 1.03 g (0.00446 mole) N-[(4-nitrophenyl)methyl]-propylamine hydrochloride in 25 mL water in a 125-mL separatory funnel. Add 15 mL 1 M NaOH and shake the mixture. Extract the N-[(4-nitrophenyl)methyl]propylamine with 50 mL toluene, and separate the phases. Add a solution of 262 µL (321 mg, 0.00184 mole) 2,4-TDI in 30 mL toluene to the solution of N-[(4-nitrophenyl)methyl]propylamine. Collect the precipitate by filtration. Purify the product by dissolving it in a small volume of dichloromethane and precipitating it with hexane. Dry the product in vacuo (MP = 136 to 139 °C).

APPENDIX C: Preparation of Reagent-Coated Glass Wool

Dissolve 300 mg (0.001 mole) N-[(4-nitrophenyl)methyl]propylamine hydrochloride in 25 mL water in a 125-mL separatory funnel. Add 15 mL 1 M NaOH and shake the mixture. Extract the N-[(4-nitrophenyl)methyl]propylamine with 50 mL hexane. Transfer 40 mL of the hexane solution to a 50-mL beaker which is wrapped with aluminum foil and contains 1.82 g silanized glass wool. Under dim light, evaporate hexane from the beaker with the aid of a stream of nitrogen. Knead the glass wool with a glass rod to produce a uniform coating. Continue to evaporate hexane until the glass wool appears dry. Protect the coated glass wool from bright light. The quantity of coated glass wool is sufficient for the preparation of the front and back sections for twenty samplers.

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DIISOCYANATES

TOLUENE-2,6-DIISOCYANATE (2,6-TDI)
1,6-HEXAMETHYLENE DIISOCYANATE (HDI)
TOLUENE-2,4-DIISOCYANATE (2,4-TDI)

Method no.:	42
Matrix:	Air
Procedure:	Samples are collected by drawing a known volume of air through glass fiber filters coated with 0.1 mg of 1-(2-pyridyl)piperazine (1-2PP) which are contained in open-face cassettes. Samples are extracted with 90/10 (v/v) acetonitrile/dimethyl sulfoxide (ACN/DMSO) and analyzed by high performance liquid chromatography (HPLC) using an ultraviolet or fluorescence detector. (The coated filters used in Method 47 for MDI are also acceptable for this procedure. Those filters are coated with 1 mg instead of 0.1 mg of 1-2PP.)
Recommended air volume and sampling rate:	15 L at a flow of 1 L/min
Special requirements:	It is recommended that coated glass fiber filters be stored at reduced temperature until used for sampling.
Status of method:	A sampling and analytical method that has been subjected to the established evaluation procedures of the Organic Methods Evaluation Branch.

Date: February, 1983

Chemist: Donald Burright

Carcinogen and Pesticide Branch
OSHA Analytical Laboratory
Salt Lake City, Utah

(Title page continued)

	2,6-TDI	HDI	2,4-TDI
Target concentration			(OSHA PEL)
µg/m³	140	140	140
ppb	20	20	20
Detection limit of the overall procedure:			
µg/m³	1.6	2.3	1.3
ppb	0.23	0.32	0.17
Reliable quantitation limit:			
µg/m³	2.3	2.9	2.5
ppb	0.32	0.43	0.36
Standard error of estimate at target concentration, % (Section 4.9.)	7.63	7.79	6.89

(Air concentrations are based on 15-L air sample volume)
(ppb = part per billion)

1. General discussion

1.1. Background

1.1.1. History of procedure

Some of the earliest procedures to determine atmospheric diisocyanate concentrations were developed by Ranta and Marcali (Ref. 5.1.). Both of these procedures are inconvenient as they use a bubbler for sampling and their colorimetric analyses are non-specific. A later sampling procedure uses p-nitrobenzyl-N-n-propylamine (nitro reagent) in toluene bubblers (Ref. 5.2.). While this method is specific for diisocyanates, it still retains the use of the bubbler and nitro reagent which is unstable when stored for long periods of time, even if it is kept at reduced temperature. The past couple of years have seen several new derivatizing reagents being used, N-methyl-1-naphthalenemethylamine (Ref. 5.3.), 9-(n-methylaminomethyl)-anthracene (Ref. 5.4.) and 1-2PP (Ref. 5.5.-5.7.). The collection procedure of these new studies all involve the use of toluene bubblers. The purpose of this study was to find a collection system that does not use a bubbler, yet retains the sensitivity, precision and accuracy of the nitro reagent method.

1-2PP is a suitable derivatizing reagent, when coated on a glass fiber filter, for several reasons:

1) The high boiling liquid is retained on a glass fiber filter and stability is not a problem.

2) The rapid and exothermic reaction with both aromatic and aliphatic diisocyanates results in derivatization on the filter (Ref. 5.7.).

3) The derivatives have higher molar absorptivities in the UV region than those formed with nitro reagent which allows the extraction volume to be larger without loss of sensitivity (Ref. 5.5.).

This procedure compares favorable when tested side-by-side with the nitro reagent method by Cummins (Ref. 5.10.) for 2,4-TDI. (Section 4.10.). Additional work is being done to study 4,4'-methylenediphenylisocyanate (MDI) and isophorone diisocyanate (IPDI) using 1-2PP as the derivatizing reagent.

1.1.2. Toxic effects (This section is for information only and should not be taken as a basis for OSHA policy.)

Continued inhalation of diisocyanate vapors or mists can cause nausea, headache, coughing, irritation of the nose and throat, shortness of breath and chest discomfort. Massive exposure can cause severe coughing spasms, bronchitis and chemical pneumonitis. Some people can become sensitized to isocyanates and may suffer asthmatic attacks and respiratory distress when subsequently exposed to very low concentrations (Ref. 5.9.). Recent studies have produced conflicting results about the mutagenicity of TDI (Ref. 5.1. and 5.9.). No data has been found to indicate that diisocyanates are carcinogenic or teratogenic (Ref. 5.1. and 5.9.).

1.1.3. Operations where exposure may occur

The manufacture of polyurethane foams, coatings, and elastomers potentially exposes a minimum of 100,000 workers to diisocyanates (Ref. 5.2.). Diisocyanates can be found in paints, insulation, adhesives, automobile bumpers, shoe soles, and hundreds of other applications (Ref. 5.2. and 5.8.). Over 700 million pounds of diisocyanates were produced in 1975 (Ref. 5.2.).

1.1.4. Physical properties

	2,6-TDI	HDI	2,4-TDI
CAS number	91-08-7	822-06-0	584-84-9
MW	174.16	168.20	174.16
BP, °C @ mm Hg	96 @ 1.5	213 @ 760	251 @ 760
MP, °C	8	-55	22
Specific gravity @ 75°C	N/A	1.05	1.22
Vapor pressure, mm Hg	N/A	0.05	0.025
Color	All colorless to pale yellow		
Odor	All sharp pungent		
Flash point (closed cup), °C	N/A	140	127

(N/A = Not Available)

Synonyms and structures - See Figure 1.1.4.

1.2. Limit defining parameters (The analyte air concentrations listed through this method are based on an air volume of 15 L and an extraction volume of 2 mL.)

1.2.1. Detection limit of the analytical procedure

The detection limit of the analytical procedure is the mass of analyte per injection which will result in a peak whose height is about five times the amplitude of the baseline noise. (Section 4.1.)

The Detection Limit of the Analytical Procedure
ng/injection

2,6-TDI	HDI	2,4-TDI
0.18	0.18	0.18

1.2.2. Detection limit of the overall procedure

The detection limit of the overall procedure is the amount of analyte spiked on the sampling device which allows recovery of an amount of analyte equivalent to the detection limit of the analytical procedure. (Section 4.2.)

The Detection Limits of the Overall Procedure

	2,6-TDI	HDI	2,4-TDI
ng/sample	24	33	19
$\mu g/m^3$	1.6	2.3	1.3
ppb	0.23	0.32	0.17

1.2.3. Reliable quantitation limits

The reliable quantitation limit is the smallest amount of analyte which can be quantitated within the requirements of at least 75% recovery and a precision (1.96 SD) of ±25% or better. The reliable quantitation limits are higher than the detection limits of the overall procedure to satisfy the precision requirement. (Section 4.3.)

The Reliable Quantitation Limits

	2,6-TDI	HDI	2,4-TDI
ng/sample	34	44	39
$\mu g/m^3$	2.3	2.9	2.5
ppb	0.32	0.43	0.36

The reliable quantitation limits and detection limits reported in the method are based upon optimization of the instrument for the smallest possible amount of analyte. When the target concentration of an analyte is exceptionally higher than these limits, they may not be attainable at the routine operating parameters.

1.2.4. Sensitivity

The sensitivity of the analytical procedure is determined by the slope of the calibration curve over a concentration range 0.5 to 2 times the target concentration. The sensitivity will vary somewhat with the particular instrument used in the analysis. (Section 4.5.)

The Sensitivity of the Analytical Procedure

	2,6-TDI	HDI	2,4-TDI
Area units per µg/mL	85600	84300	159000

1.2.5. Recovery

The recoveries of the analytes from samples used in the 18-day storage tests remained above the values presented below. These values are determined from the calculated regression lines of the storage graphs. (Section 4.9.)

Recovery, %

T °C	2,6-TDI	HDI	2,4-TDI
-25	86.3	81.1	81.3
22	86.4	83.0	80.3

The recovery of analyte from the collection medium during storage must be 75% or greater.

1.2.6. Precision (Analytical method only)

The pooled coefficients of variation obtained from replicate determinations of analytical standards at 0.5, 1 and 2 times the target concentration are presented below. (Section 4.4.)

The Pooled Coefficients of Variation

2,6-TDI	HDI	2,4-TDI
0.009	0.013	0.009

1.2.7. Precision (Overall procedure)

The overall procedure must provide results at the target concentrations that are ±25% or better at the 95% confidence level. The precisions at the 95% confidence level for the 18-day storage test are presented below. (Section 4.9.) The reported values each include an additional ±5% for sampling error.

Precision at the 95% Confidence Level, %

2,6-TDI	HDI	2,4-TDI
14.9	15.2	13.5

1.2.8. Reproducibility

Five samples, prepared by vapor spiking, and a draft copy of this procedure were given to a chemist unassociated with this evaluation. The samples were analyzed after 6 days of storage at -25°C. The data listed below are corrected for extraction efficiency (Section 4.8.).

Recovery %

	2,6-TDI	HDI	2,4-TDI
$\bar{X}$	101.5	100.4	105.4
SD	1.6	2.0	2.4

1.3. Advantages

1.3.1. The sampling and analytical procedures are specific and sensitive for several diisocyanates employed in industry (Ref. 5.7.).

1.3.2. The collection system is less cumbersome than the use of a bubbler.

1.3.3. 1-2PP is more stable and less expensive than p-nitrobenzyl-N-n-propylamine, (nitro reagent).

1.4. Disadvantages

The use of peak ratios to confirm low concentrations of diisocyanates is impractical due to the small response at 313 nm.

2. Sampling procedure

2.1. Apparatus

2.1.1. Samples are collected by use of a personal sampling pump that can be calibrated to within [illegible]% at the recommended flow rate with the sampling device in line.

2.1.2. A three-piece styrene cassette containing a glass fiber filter coated with 0.1 mg of 1-2PP and a backup pad. (See Fig. 4.13.1.)

2.1.3. Coated filters are prepared by applying 0.5 mL of a solution of 0.2 mg/mL 1-2PP in methylene chloride to each glass fiber filter. The wet filters are allowed to air dry before placing in a jar. Vacuum is applied to the jar to remove residual methylene chloride. (The coated filters used in Method 47 for MDI are also acceptable for this procedure. These filters are coated with 1 mg of 1-2PP and are prepared as above except a 20 mg/mL solution of 1-2PP in methylene chloride is used.)

2.1.4. Coated filters should be stored at reduced temperature as a precaution.

2.2. Reagents

None are required.

2.3. Sampling technique

2.3.1. Remove the inlet cover from the three-piece cassette. Save cover for installation after sampling.

2.3.2. Attach the cassette in the breathing zone of the employee to be monitored.

2.3.3. The recommended flow rate is 1 L/min with a recommended total air volume of 15 L.

2.3.4. After sampling for the appropriate time, remove the sampling device and reinstall the small plug and inlet cover.

2.3.5. Wrap each sample end-to-end with an OSHA Form 21 seal.

2.3.6. With each set of samples, submit at least one blank sample. The blank should be subjected to the same handling as the samples except that no air is drawn through it.

2.3.7. Bulk samples submitted for analysis must be shipped in sealed vials and in a separate container.

2.4. Retention efficiency

2.4.1. Experimental design

Due to present laboratory limitations, controlled test atmospheres of diisocyanates cannot effectively be generated. However, the following procedure using a vapor spiking technique was used as an alternative to study analyte retention. This was done to approximate the recommended open-face collection of diisocyanates.

A glass syringe barrel equipped with a Luer taper tip was silanized and silanized glass wool was placed into the syringe. The Luer tip was inserted into the inlet part of a cassette so that the tip was flush with the inside surface of the cassette. The other end of the syringe was attached to a sampling port. The outlet of the cassette was attached to a vacuum pump. A critical orifice between the cassette and the pump maintained a constant 1 L/min flow rate.

Dry air samples were prepared by attaching a dry air source to a manifold inlet. Humid air samples were generated by passing air through water in a controlled temperature water bath. The humidity was monitored in the sampling manifold via a humidity probe. The glass wool was spiked with diisocyanate in methylene chloride. The desired quantity of air was then drawn through the glass wool, at a flow rate of 1 L/min, and onto the coated filter, which was analyzed to determine analyte loss.

2.4.2. Retention results

Humidity has an effect on the ability of a glass fiber filter to retain derivatized diisocyanates. When a sample of ten times the target concentration is vapor generated and 200 L of dry air (12% humidity) is drawn through the filter, an average of 95.4% of the diisocyanates is found on the coated filter. Only 1.2% is found on the backup pad.

When higher relative humidity (R.H.) is added to the sampling system, a different result is obtained. Samples,

vapor spiked with 20 L of dry air at the target concentration and with humid air (78% R.H.) pulled through the cassettes at several known air volumes, show a loss of diisocyanate derivative. Based on an extrapolation of these results, the recommended maximum air volume should be 80 L. Exceeding this amount could result in less than 75% recovery of the diisocyanate entering the cassette. (Section 4.6.)

2.5. Extraction efficiency

The average extraction efficiency for each of the analytes spiked at the target concentration on a coated glass fiber filter is presented below. (Section 4.7.)

Average Extraction Efficiencies, %

2,6-TDI	HDI	2,4-TDI
91.2	93.3	90.8

2.6. Recommended air volume and sampling rate

2.6.1. The recommended air volume is 15 L.

2.6.2. The recommended air sampling rate is 1 L/min.

2.7. Interferences

Any compound, that could be collected on the glass fiber filter that could react with the 1-2PP or compete with it in the reaction to derivatize the diisocyanate, should be considered as an interference. Potential interferences include anhydrides, amines, alcohols and carboxylic acids.

2.8. Safety precautions

The sampling equipment should be attached to the worker in such a manner that it will not interfere with work performance or safety.

3. Analytical Procedure

3.1. Apparatus

3.1.1. High performance liquid chromatograph equipped with UV detector, manual or automatic sample injector, and chart recorder.

3.1.2. HPLC stainless steel column capable of separating diisocyanate derivatives. The column employed in this

study was a 25 cm x 4.6 mm ID stainless steel column packed by Alltech with 10 micron C_{18}.

3.1.3. An electronic integrator, or some other suitable method of determining peak areas.

3.1.4. Vials, 4-mL with Teflon-lined caps.

3.1.5. Syringes, of convenient sizes for sample and standard preparations and injections.

3.1.6. Volumetric pipettes and flasks for preparation of standards.

3.1.7. Suitable glassware for preparation of diisocyanate urea derivatives.

3.1.8. Micro-analytical balance used to weigh standard preparations.

3.2. Reagents

3.2.1. HPLC grade methylene chloride, hexane, acetonitrile, and dimethyl sulfoxide.

3.2.2. HPLC grade water. Our laboratory employs a commercially available water filtration system for the preparation of HPLC grade water.

3.2.3. 1-(2-Pyridyl)piperazine, Aldrich, Milwaukee, WI.

3.2.4. 2,6-TDI, Carbolabs, Inc., New Haven, CT.

3.2.5. HDI, Aldrich, Milwaukee, WI.

3.2.6. 2,4-TDI, Eastman Chemicals, Rochester, NY.

3.2.7. HPLC grade ammonium acetate.

3.2.8. Glacial acetic acid.

3.3. Standard preparation

3.3.1. A solution containing 3.5 g of 2,4-TDI in 25 mL of methylene chloride is slowly added to a stirred solution of 7.25 g of 1-2PP in 100 mL of methylene chloride. The solution is then heated to 35°C for 10 minutes. The product is precipitated with hexane, (precipitation may start without adding hexane), filtered, redissolved in a minimal volume of methylene chloride and reprecipitated. The precipitate is filtered and washed with hexane

(approximate yield is 9 g of the derivative after being dried by vacuum). This preparation is a modification of the procedure reported by Goldberg et al (Ref.). Derivatives of the two other diisocyanates are prepared by a similar procedure.

3.3.2. Preparation of working range standards

A stock standard solution is prepared by dissolving the diisocyanate derivatives into DMSO. To express the derivative as free diisocyanate, the amount of 2,4-TDI and 2,6-TDI ureas weighed is multiplied by the conversion factor 0.3479

$$\frac{\text{MW TDI}}{\text{MW urea}} = \frac{174.16}{500.61} = 0.3479$$

Similarly, the conversion factor for HDI urea is 0.3400

$$\frac{\text{MW HDI}}{\text{MW urea}} = \frac{168.20}{494.64} = 0.3400$$

All dilutions of the stock solutions are made with acetonitrile to arrive at the working range.

3.4. Sample preparation

3.4.1. The styrene cassette is opened and the glass fiber filter is placed into a 4-mL vial so that the filter is flat against the inside surface of the vial, not folded or crumpled.

3.4.2. Two mL of the extracting solution, 90/10 (v/v) ACN/DMSO, are added.

3.4.3. A cap equipped with a Teflon liner is installed.

3.4.4. The vial is shaken to remove large air bubbles from between the filter and the glass. Let the vial set for one hour.

3.5. Analysis

3.5.1. Reverse phase HPLC conditions

Column:	25 cm x 4.7 mm ID stainless steel column packed with 10 micron All-tech C_8 or suitable equivalent.
Mobile phase:	0.01 M ammonium acetate in 37.5/62.5 ACN/water (v/v) adjusted to pH 6.2 with acetic acid
Flow Rate:	1 mL/min
UV Detector:	254 and 313 nm
Fluorescence Detector:	240 nm excitation 370 nm emission
Injection size:	10-25 µL

3.5.2. Chromatograms (Section 4.11.)

3.5.3. An external standard procedure is used to prepare a calibration curve using at least 2 stock solutions from which dilutions are made. The calibration curve is prepared daily. The samples are bracketed with analytical standards.

3.6. Interferences

3.6.1. Any compound having the same retention time as the analyte is a possible interference. Benzaldehyde is an interference for 2,4-TDI urea using the aforementioned analytical conditions but is not normally expected to be found. Generally, chromatographic conditions can be altered to separate an interference.

3.6.2. Compounds that can react with a diisocyanate represent a potential interference. These include molecules containing the following functional groups: amines, alcohols, phenols, and carboxylic acids. Compounds, such as anhydrides, that will react with 1-2PP should be considered as potential interferences also.

3.6.3. Retention time on a single column is not proof of chemical identity. Analysis by an alternate column system, ratioing of wavelength response, and mass spectrometry are additional means of identity. (See UV spectra for diisocyanate derivatives, Figures 4.12.1.-4.12.3.)

3.7. Calculations

The concentration in µg/mL of diisocyanate present in a sample is determined from the area response of the analytes as measured by an electronic integrator or peak heights. Comparison of sample response with a least square curve fit for standards allows the analyst to determine the concentration of diisocyanate in µg/mL for the sample. Since the sample volume is 2 mL, the results in µg/m³ of air are expressed by the following equation:

µg/m³ = (µg/mL)(2 mL)/(m³ of air sampled)(Extraction Eff.)

3.8. Safety precautions

3.8.1. Avoid skin contact with all solvents.

3.8.2. Wear safety glasses at all times.

3.8.3. Avoid exposure to the diisocyanates standards.

4. Backup data section

4.1. Detection limit of the analytical procedure

The detection limit of the analytical procedure was 0.18 ng for all three analytes. This amount produced a peak whose height was about 5 times the height of the baseline noise. The injection size recommended in the analytical procedure (10 µL) was used in the determination of the detection limit for the analytical procedure. (Figure 4.1.).

4.2. Detection limit of the overall procedure

4.2.1. The following data were obtained by vapor spiking increasing amounts of the analytes onto sampling devices. The injection size recommended in the analytical procedure (25 µL) was used to determine the detection limit of the overall procedure.

FORMULA: TDI: $CH_3C_6H_3(NCO)_2$
MDI: $CH_2(C_6H_4NCO)_2$
HDI: $OCN(CH_2)_6NCO$
M.W.: TDI 174.16; MDI 250.26; HDI 168.20

ISOCYANATES
METHOD: 5521
ISSUED: 5/15/89

OSHA/NIOSH/ACGIH: Table 1

PROPERTIES: Table 1

SYNONYMS: Table 1

SAMPLING

SAMPLER: IMPINGER
(solution of 1-(2-methoxyphenyl)-piperazine in toluene)

FLOW RATE: 1 L/min

VOL-MIN: 5 L @ 35 µg TDI/m^3
-MAX: 500 L

SHIPMENT: ship in screw-cap vial refrigerated @ 4 °C or lower

SAMPLE STABILITY: may be unstable; perform steps 8 & 9 as soon as possible

FIELD BLANKS: 10% of samples

ACCURACY

RANGE STUDIED: not studied

BIAS: not known

OVERALL PRECISION (s_r): not known

MEASUREMENT

TECHNIQUE: HPLC, ELECTROCHEMICAL and UV DETECTION

ANALYTE: urea derivatives of isocyanates

SAMPLE PREP: acetylate excess reagent, evaporate toluene, redissolve in 5 mL CH_3OH

INJECTION VOLUME: 10 µL

MOBILE PHASE: acetonitrile (20% to 40%)/pH 6.0 methanolic buffer (80% to 60%); 1 mL/min; ambient temperature

COLUMN: Supelcosil, LC-8-DB, 3-µm particle size, 7.5 cm x 4.6 mm; 2-cm guard column, 10-µm particle size

DETECTORS: UV, 242 nm; ECHD, + 0.80 V vs. Ag/AgCl

CALIBRATION: standard solutions of ureas in methanol

RANGE: 2,4-TDI: 0.5 to 8 µg per sample
2,6-TDI: 0.7 to 10 µg per sample
MDI: 0.3 to 4 µg per sample
HDI: 1 to 15 µg per sample

ESTIMATED LOD: ca. 0.1 µg diisocyanate per sample

PRECISION (s_r): not determined

APPLICABILITY: The working range is from 5 µg/m^3 2,4-TDI, 7 µg/m^3 2,6-TDI, 3 µg/m^3 MDI, and 1 µg/m^3 HDI to more than 1 mg/m^3 for 100-L air samples. This method determines the air concentration of specific diisocyanates. The method is only qualitative for polyisocyanates, as it gave low evaluation results with both polyisocyanates used. The method has been applied to samples from general foaming, spray- or dip-painting industries [1].

INTERFERENCES: Any substance which elutes with the ureas and absorbs ultraviolet light or is electroactive will interfere with the analysis. Mobile phase conditions can be adjusted to separate most co-eluting peaks, however, ureas of HDI and TDI are difficult to separate.

OTHER METHODS: This method is a modification of Method MDHS 25 published by the Health and Safety Executive of Great Britain [2,3]. Method 2535 is an alternate method for TDI vapor, employing collection on glass wool impregnated with N-(4-nitrophenylmethyl)propylamine.

REAGENTS:

1. 1-(2-Methoxyphenyl)piperazine*, 98%.
2. Acetic annydride, reagent grade.
3. Methanol, HPLC grade.
4. Acetonitrile, HPLC grade.
5. Water, deionized, distilled.
6. Sodium acetate, annydrous.
7. Acetic acid, glacial.
8. Nitrogen, 99.995%.
9. Toluene, HPLC grade.
10. Sampling medium, 1-(2-methoxyphenyl)piperazine in toluene, 43 mg/L.
11. Ureas derived from the isocyanate. (See APPENDIX).
12. Dimethyl sulfoxide, reagent grade.
13. Mobile phase, acetonitrile and buffer solution to achieve appropriate mobile phase.
14. Buffer solution. Dissolve 15 g anhydrous sodium acetate in 1 L distilled-deionized water. Add 1 L methanol. Add glacial acetic acid to bring pH to 6.0.
15. Urea calibration stock solution, 0.01 µg/µL urea in methanol.
16. Reagent calibration stock solution, 1.0 µg/µL 1-(2-methoxyphenyl)-piperazine in methanol.
17. Helium, prepurified.

*See SPECIAL PRECAUTIONS

EQUIPMENT:

1. Sampler: Midget impinger, 25-mL.
2. Personal sampling pump, 1.0 L/min, with flexible connecting tubing free of phthalate plasticizer.
   NOTE: Avoid collection of plasticizer in the toluene during sampling. Fluran™ tubing is an acceptable tubing.
3. Liquid chromatograph (HPLC) with ultraviolet (UV) detector (242 nm) and electrochemical (ECHD) detector (+ 0.80 V vs. Ag/AgCl), recorder, integrator and column (page 5521-1).
4. Ultrasonic water bath.
5. Vials, 4-mL glass, with screw caps and 20-mL glass, screw caps with cone-shaped polyethylene liner and shrinkable sealing bands.
6. Pasteur pipets, 7-cm glass, disposable.
7. Flasks, volumetric, glass, 10-mL.
8. Syringes, sizes appropriate for preparing standard solutions.
9. Pipets, 5- and 15-mL glass, delivery, with pipet bulb.
10. Hot plate, spark free, 60 °C.
11. Evaporator, Mini-Vap, 6-port or equivalent.
12. pH meter.
13. Vacuum oven.
14. Buchner funnel, fritted glass, medium porosity, 100-mL.
15. Vacuum pump.
16. Flask, filtration, 500-mL.

SPECIAL PRECAUTIONS: Preparation of urea derivatives, samples, and standards should be done in hood to avoid exposure to isocyanate and solvent vapors. Isocyanates are known respiratory irritants. Toxicity of 1-(2-methoxyphenyl)piperazine is unknown.

SAMPLING:

1. Calibrate each personal sampling pump with a representative sampler in line.
2. Transfer 15 mL sampling medium to an impinger.
3. Connect the assembled impinger to a sampling pump.
4. Sample 5 to 500 L of air at 1.0 L/min.
   NOTE 1: Toluene evaporates during sampling; when level of solution drops below 10 mL, restore volume to 15 mL with toluene.
   NOTE 2: The reagent in the sampling medium reacts with isocyanates to form ureas:

$$CH_3OC_6H_4NC_4H_4NH + R\text{-}N{=}C{=}O \rightarrow CH_3OC_6H_4NC_4H_4NC(=O)NHR$$

5. Prepare blank samples by transferring 15 mL sampling medium to 20-mL vials.
6. Transfer the sample solution to a 20-mL vial for shipment. Rinse both impinger parts with 2 to 3 mL toluene and add rinsings to the sample. Secure vial's screw cap with sealing band. Refrigerate samples as soon as possible. If samples are to be shipped, carefully pack the vials to avoid breakage or spillage of sample.

7. Obtain a bulk sample (1 to 2 mL) of and the material safety data sheet for any polyisocyanate used at the worksite. Analysis of samples prepared from this bulk material will be useful for identifying ureas derived from the polyisocyanate.

SAMPLE PREPARATION:

8. Add 25 µL acetic anhydride to acetylate the excess 1-(2-methoxyphenyl)piperazine remaining in the sample solution, to provide for efficient chromatography.
   NOTE: The acetylation reaction is:

$$CH_3OC_6H_4NC_4H_4NH + CH_3C(=O)OC(=O)CH_3 \rightarrow CH_3OC_6H_4NC_4H_4NC(=O)CH_3 + CH_3C(=O)OH$$

9. Evaporate the acetylated sample to dryness under a gentle stream of nitrogen while warming to 60 °C on a hotplate.
10. Redissolve the residue in 5.0 mL methanol, while agitating the sample in an ultrasonic water bath for 15 min.

CALIBRATION AND QUALITY CONTROL:

11. Prepare working standards containing 0.01 to 4.0 µg/mL of the appropriate urea(s) (TDIU, HDIU, and/or MDIU) and 100 µg/mL of 1-(2-methoxyphenyl)piperazine by adding aliquots of calibration stock solutions to 2 mL methanol in a 10-mL volumetric flask. Add 10 µL acetic anhydride to each standard. Mix and dilute to the mark with methanol.
    NOTE: The standard solutions need include only ureas derived from the diisocyanates expected in the air samples and, if polyisocyanates are of interest, ureas derived from the diisocyanates structurally most similar to the polyisocyanates.
12. Analyze working standards together with samples and blanks (steps 15 through 17). Prepare a calibration graph for the urea in terms of quantity of isocyanate group, M (ECHD area vs. µmol of isocyanate group per sample). Molecular weights of typical ureas are: TDIU = 558.7 g/mol; MDIU = 634.8 g/mol; HDIU = 552.7 g/mol).

$$M = \frac{(C)\bullet(N)\bullet(5)}{MW}, \text{ µmol/sample}$$

Where: M is the quantity of isocyanate group per sample (µmol)
C is the concentration of urea in the standard solution (µg/mL)
N is the number of isocyanate groups per molecule (eg, 2 for a diisocyanate)
5 is the liquid volume of a sample (mL)
MW is the molecular weight of the urea

13. Prepare control samples by adding 0.1, 1.0 and 10.0 µg of urea to 15 mL sampling medium. Prepare these samples for analysis (steps 8 through 10).
14. Prepare qualitative samples from bulk polyisocyanate. Using information from the container or the material safety data sheet, add enough polyisocyanate to react with approximately 1/10 to 1/3 of the reagent in 15 mL of sampling medium. Prepare samples for analysis (in steps 8 through 10) and analyze. Use the chromatographic data for aid in indentifying peaks of ureas derived from polyisocyanates.

MEASUREMENT:

15. Set up the HPLC system according to manufacturer's recommendations and to the conditions given on page 5521-1.
16. Inject a 10-µL aliquot of the sample solution from step 10. Capcity factors for the urea derivatives are:

Isocyanate	Mobile Phase: Acetonitrile	Mobile Phase: buffer Solution	Capacity factor (k')[a]
2,4-TDI	30%	70%	2
MDI	35%	65%	4
PMPPI[b]	35%	65%	10
2,4-TDI	40%	60%	3
HDI	40%	60%	3
HDI-Biuret[c]	40%	60%	6
$(HDI)_3$ [d]	40%	60%	8

[a] $k' = (t_r - t_0) / t_0$, where t_r is the retention time of the urea and t_0 is the retention time of an unretained compound.
[b] One or several oligomers of polymethylenepolyphenyl isocyanate.
[c] 1,3,5-Tris(6-isocyanatohexyl)biuret.
[d] 1,3,5-Tris(6-isocyanatohexyl)hexahydro-1,3,5-triazin-2,4,6-trione.

17. Measure peak area with both detectors.
    NOTE 1: Use ECHD response for quantitation of ureas.
    NOTE 2: The ureas from the polyisocyanates are identified (step 19) by the ratio of their response to electrochemical and ultraviolet detection. These ratios are similiar in value to the ratio of the urea from the diisocyanate to which the polyisocyanate is structurally related.

CALCULATIONS:

18. Calculate the ratio of the electrochemical detector response to the ultraviolet detector response for all peaks in the chromatogram.
19. Identify as a polyisocyanate-derived urea any peak in the samples for which the ratio is between 0.75 and 1.5 times the average ratio given by the urea of the structurally similar diisocyanate in calibration standards.
20. Read from calibration graph the quantity, M (µmol per sample), of isocyanate group for the urea from the isocyanate of interest.
21. Calculate the concentration of the specific isocyanate of interest, C_M ($\mu g/m^3$), in the air volume sampled, V (L):

$$C_M = M \bullet MW \bullet 10^3 / N \bullet V, \quad \mu g/m^3$$

Where: MW is the molecular weight of isocyanate
N is the number of isocyanate groups per molecule

EVALUATION OF METHOD:

The stability of 2,4-TDIU in toluene was investigated using groups of six samples stored at room temperature for up to two weeks or at 4 °C for 1 week with the following results:

Quantity (µg)	Storage Period (days)	Storage Temperature	Percent Recovery, 95% Confidence Interval
1.9	0	room	99 ± 11
3.8	0	room	98 ± 4
1.9	7	room	78 ± 7
1.9	7	4 °C	88 ± 7
3.8	7	room	67 ± 6
3.8	14	room	70 ± 11

The data demonstrate sample instability at room temperature (about 22 °C) and suggest that the samples are somewhat unstable even at 4 °C.

Estimates of the limits of quantitation (LOQs) (expressed in terms of the quantity of diisocyanate per sample) were made from the electrochemical-detector calibration curves used for the analysis of field samples or control samples: 2,4-TDI, 0.5 µg [1, Sequence 6043]; 2,6-TDI, 0.7 µg [1, Sequence 6043]; MDI, 0.3 µg [1, Sequence 6019]; HDI, 1 µg [4]. The corresponding limits of detection (LODs) were: 2,4-TDI, 0.2 µg; 2,6-TDI, 0.2 µg; MDI, 0.09 µg; HDI, 0.3 µg. Because the polyisocyanates for which authentic standards are not available must be identified by the ratio of the electrochemical-detector and UV-detector responses, the detection limits for these substances depend upon the less sensitive UV detector and, thus, will be higher.

The use of the ratio of detector responses to identify ureas formed from polyisocyanates and the estimation of polyisocyanate concentration by comparing to diisocyanate standards were evaluated using samples of commercial isocyanates, which were MDI- or HDI-based polyisocyanates, reagent grade HDI, and a solution of 80% 2,4-TDI and 20% 2,6-TDI. The MDI-based commericial product, MF184, was reported to be 50% polymethylenepolyphenyl isocyanate and 50% MDI. The HDI-based commercial product was reported to be 44% of the trimer, 1,3,5-tris(6-isocyanatohexyl)hexahydro-1,3,5-triazin-2,4,6-trione [$(HDI)_3$], with no HDI present. Fifty-six samples were prepared and analyzed for isocyanate, 15 from MF184, 12 from $(HDI)_3$, 11 from HDI, and 18 from TDI. The range of isocyanate group present was 0.078 - 1.7 µmol per sample as determined from the measurement of the isocyanate by weight or volume. The average recoveries for these samples using the procedure described in the metnod were 61% for MF184, 54% for $(HDI)_3$, 123% for HDI, and 90% for TDI.

The precision of the average ratio of the response of the electrochemical detector to the response of the ultraviolet detector was determined from the standard-curve data for the two detectors. The relative standard deviations were 21%, 12%, and 14% for 2,4-TDIU, MDIU, and HDIU, respectively. The average values of the ratios vary with the HPLC mobile phase conditions used for analysis.

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[2] "MDHS 25: Methods for the Determination of Hazardous Substances, Organic Isocyanates in Air. Laboratory Method Using 1-(2-Methoxyphenyl)piperazine Solution and High Performance Liquid Chromatography," Occupational Medicine and Hygiene Laboratory, Health and Safety Executive, London, U.K. (1987).

[3] Bagon, D. A., C. J. Warwick, and R. H. Brown, Am. Ind. Hyg. Assoc. J. 45: 39-43(1984).

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METHOD WRITTEN BY: M. J. Seymour and A. W. Teass, NIOSH/DPSE

Table 1: Synonyms, exposure limits, and properties

Compounds (Synonyms)	Exposure Limits, µg/m³*			Properties
	(OSHA)	(NIOSH)	(ACGIH)	
2,4-TDI (2,4-TDI; 2,4-Toluene diisocyanate; CAS # 584-84-9)	40	40** 150 STEL	40	liquid; d 1.224 g/mL @ 20 °C; BP 251 °C; VP 1.3 Pa (0.01 mm Hg) @ 20 °C; MP 19.5 - 21.5 °C
2,6-TDI (2,6-TDI; CAS # 91-08-7)	None	40** 150 STEL	None	liquid; d 1.22 g/mL @ 20 °C; VP 1.3 Pa (0.01 mm Hg) @ 20 °C
MDI (4,4'-methylenediphenyl isocyanate; diphenyl-methane-4,4'-diisocyanate; methylenebis(phenyl isocyanate); CAS # 101-68-8)	200 (ceiling)	50 200 (ceiling)	200 (ceiling)	solid (fused); d 1.198 g/mL @ 70 °C; MP 37.2 °C; VP 0.04 Pa @ 24 °C
HDI (Hexamethylene diisocyanate; CAS # 822-06-0)	None	35 140 (ceiling)	35	liquid; d 1.04 g/mL @ 20 °C; BP 255 °C
Polyisocyanates (Prepolymers; the biuret derived from HDI; cyclic trimer of HDI; isocyanate-bearing polyurethanes)	None	None	None	refer to material safety data sheet

* 1 ppm = 7100 µg/m³ TDI; 10208 µg/m³ MDI; 7350 µg/m³ HDI; **Carcinogen

APPENDIX: PREPARATION OF UREA DERIVATIVE

Dissolve 0.005 mole (1 g) of 1-(2-methoxyphenyl)piperazine in 25 mL dimethyl sulfoxide. Dissolve 0.002 mole (350-500 mg) of isocyanate in 25 mL dimethyl sulfoxide. Over a period of 1-2 min, gradually add the isocyanate solution to the stirred derivatizing reagent solution. Warm the resulting solution to 60-90 °C and continue to stir for at least 30 min. Discontinue heating of the solution and add 300 mL deionized water. The urea will precipitate as a white solid. Stop stirring after addition of water. Collect the urea in a fritted-glass Buchner funnel by suction filtration. Dry the compound in a vacuum oven at 75 °C to remove water. Recrystallize until a constant melting point is obtained.

To recrystallize urea, add toluene (150 mL) to dried urea and warm mixture to 60 °C. Slowly and very carefully add just enough methanol (BP 65 °C) to completely dissolve the urea. Remove from heat and allow to cool. Collect the crystals by suction filtration and dry them in vacuum oven at 35 °C. The urea derivatives and their melting points are as follows:

Diisocyanates	Urea Derivatives	MP (°C)
2,4-TDI	N,N'-bis[4-(2-methoxyphenyl)piperazine-1-carbonyl]-2,4-toluenediamine (2,4-TDIU)	212-213 (platelets)
2,6-TDI	N,N'-bis[4-(2-methoxyphenyl)piperazine-1-carbonyl]-2,6-toluenediamine (2,6-TDIU)	231-233 (platelets)
MDI	N,N'-bis[4-(2-methoxyphenyl)piperazine-1-carbonyl]-4,4'-methylenedianiline (MDIU)	209-210 (needles)
HDI	N,N'-bis[4-(2-methoxyphenyl)piperazine-1-carbonyl]-hexamethylenediamine (HDIU)	199-200 (needles)

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